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REVIEW ARTICLE

Current Status of Tamoxifen Use: An Update for the Surgical Oncologist

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The surgical oncologist is frequently responsible for the screening and diagnosis of women with breast cancer. In this pivotal role, they are often the first to discuss treatment options, including nonsurgical interventions, with breast cancer patients. Recent long-term clinical trial data provide support for the use of tamoxifen to prevent breast cancer in women at high risk of the disease. A breast cancer risk assessment can help identify women at higher than average risk for the disease, who may be appropriate candidates for chemoprevention. It is important for the surgical oncologist to understand the current indications and evidence regarding the use of tamoxifen for breast cancer prevention and treatment as they counsel their patients on available options.

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INTRODUCTION

From the initial assessment of breast cancer risk factors to the early diagnosis of metastatic lesions, surgical oncologists are involved in every aspect of breast cancer care. Because of this, it is extremely important that we have a basic understanding of many aspects of breast cancer care traditionally relegated to the medical oncologist. Perhaps most important to the surgeon is a fundamental understanding of therapies for which the indications for usage have recently changed. Unequivocally, one of the most dramatic evolutions in the recent history of breast cancer has been that of the indications for tamoxifen use. Thus, this is an appropriate time to review many aspects of this medication in detail. In order to clarify tamoxifen's current role, this review will describe its basic mechanisms of action, outline the major studies supporting its current application in breast cancer management, and discuss its appropriate use in various situations.

MECHANISM OF ACTION

The traditional view of tamoxifen's mechanism of action has been that it is an antiestrogen. In breast tissue, this is certainly the case, with tamoxifen inhibiting growth normally stimulated by estrogens [1,2]. The *trans*-isomer form in which tamoxifen is currently marketed has significant affinity for estrogen receptors, which are nuclear transcription factors present in normal breast tissue and about two-thirds of breast cancers. In breast tissue, tamoxifen exerts antiestrogenic effects through competitive inhibition at the level of the estrogen receptor. The result of the tamoxifen-receptor complex appears to be a halting of cell proliferation in the G1 phase of the cell cycle and a slight increase in cell loss. Its overall effect on breast cancer cell proliferation is that of a cytostatic rather than a cytotoxic agent [2].

In other tissues, the tamoxifen–estrogen receptor interaction previously described may exhibit estrogen agonist properties, stimulating the tissue of concern in the same manner as estrogen. Thus, tamoxifen is perhaps better named a selective estrogen receptor modulator

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rather than an antiestrogen [3]. The estrogen agonist action appears to be responsible for some of the beneficial effects of tamoxifen, such as improved lipid profiles and bone densities, as well as the deleterious effect of an increase in endometrial proliferation.

In the breast, additional mechanisms for antitumor effects of tamoxifen exist. The estrogen receptor pathway is believed to mediate immune responses through an increase in natural killer cell activity, an increase in antibody production, and an inhibition of suppressor T-cells [4–6]. Likewise, tamoxifen has been shown to affect various growth factors. It appears to decrease levels of insulin-like growth factor 1(IGF-1), a known stimulant to breast cancer cell growth, and to increase levels of the IGF-binding proteins. Furthermore, tamoxifen appears to increase the production of growth factors that inhibit breast cancer cell growth; of these factors, the most significant is transforming growth factor-β[10].

TAMOXIFEN USE IN BREAST CANCER

As is the case with the majority of new chemotherapeutic agents, the initial trials of tamoxifen were performed in patients with stage IV disease. In 1977, the US Food and Drug Administration approved the use of tamoxifen for the treatment of metastatic breast disease in postmenopausal women [1]. This approval followed the early findings suggesting its activity in advanced breast cancer patients [11]. Further studies have now clearly documented that as many as 50% of women with estrogen receptor–positive (ER^+) metastatic breast cancer will have regression of their tumors for significant periods of time when treated with tamoxifen [12–15].

At the same time as these studies were ongoing, many groups were investigating the use of adjuvant chemotherapy to reduce the risk of and delay the onset of recurrence after surgery for node-positive breast cancer [16–18]. Prior to these trials, surgery and radiation had been the only methods of treating localized breast cancer. Although these two modalities provided adequate local control, studies clearly demonstrated decreased disease-free and overall survival in patients in whom there was lymph node involvement [19,20]. While the likelihood of remaining disease-free at 10 years after postdiagnosis was 72–76% in patients without lymph node involvement, only 35–48% of those with lymph node involvement remained disease-free at 10 years. The impact that adjuvant chemotherapy would have on these findings was addressed in two large trials. Both the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial of L-phenylalanine mustard and the Italian trial of cyclophosphamide, methotrexate, and 5-fluorouracil demonstrated a significant impact of adjuvant therapy on both disease-free and overall survival. Unfortunately, the benefits of the chemotherapy regimens used in these trials came at the expense of some toxicity. Thus, enthusiasm existed for evaluating medications that might have an impact similar to that of chemotherapy on recurrence and survival rates but without significant toxicity.

Hormonal manipulation with an agent such as tamoxifen appeared ideal, almost a natural extension of trials that had attempted to address such manipulation through ovarian ablation with oophorectomy [21]. While these initial trials were primitive, suffering from a lack of availability of hormone receptor assays and also the inappropriate inclusion of both pre- and postmenopausal patients, almost all studies demonstrated an improvement in overall survival. Using these studies for justification, trials of tamoxifen therapy in an adjuvant setting for node-positive breast cancer were undertaken. In the first trials of tamoxifen as single-agent therapy for early-stage breast cancer, the medication was prescribed for relatively short periods and only in postmenopausal women [22,23]. However, even when used for as short period as 1 year, tamoxifen had a beneficial effect on both disease-free and overall survival.

While the majority of trials of adjuvant therapy, including those of tamoxifen as a single agent, demonstrated an impact in breast cancer patients with node-positive disease, the benefit of therapy in node-negative patients was less evident. In fact, in 1985 the National Institutes of Health Consensus Conference on the Adjuvant Treatment of Breast Cancer concluded that there was not enough evidence to support the use of adjuvant chemotherapy or tamoxifen therapy in node-negative breast cancer patients [24]. This recommendation was based on the available data, which, at that time, failed to demonstrate any significant improvement in either disease-free or overall survival. However, by 1988, the National Cancer Institute had issued a clinical alert retracting its earlier statements and concluding that adjuvant therapy for node-negative patients was appropriate [25]. By this time, earlier trials had matured enough to definitively demonstrate an impact of adjuvant chemotherapy with combination medications on disease-free and overall survival [26–31].

As was the case with node-positive breast cancer, trials addressing the use of tamoxifen alone in node-negative patients were being performed concurrently with systemic chemotherapy trials. Initial reports from the Nolvadex Adjuvant Trial Organization (NATO), which randomized 605 postmenopausal, node-negative patients to a control group or a group receiving 20 mg of tamoxifen daily for 2 years, showed that there was a clear reduction in the observed to expected risk for subsequent breast cancer events in patients who had taken tamoxifen for as little as 1 year [32]. Even more significant in demonstrating the impact of tamoxifen on node-negative breast cancer patients was the NSABP B-14 trial, which included over 2,000 women under age 70 with primary operable breast cancer [32]. In preliminary analyses, there was a

36% reduction in the risk of relapse in the population treated with tamoxifen as a single agent.

A natural extension of the trials regarding both adjuvant chemotherapy and adjuvant tamoxifen therapy was an evaluation of the merit of using adjuvant tamoxifen after a patient had received systemic chemotherapy. Initial results of studies designed to address this question failed to reveal any benefit of the addition of tamoxifen to systemic chemotherapy in premenopausal women [33–36]. In fact, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), a worldwide group of collaborators formed to address the appropriate use of various therapies for breast cancer, found in a meta-analysis in 1992 that the addition of tamoxifen to systemic chemotherapy in premenopausal women, while having some effect, was certainly significantly less effective than its use as a single agent in older women [37]. Because of this, there was no standardized recommendation for its use in the premenopausal patient.

TABLE I. Proportional Recurrence and Mortality Reductions After 10 Years of Follow-up According to Tamoxifen Therapy Duration and Estrogen Receptor (ER) Status*

	Proportional reduction at 10 years (%)		Risk reduction for new primary cancer at 10 years (%)[a]
	Recurrence	Mortality	
ER^+			
Length of therapy			
1 year	21	14	13
2 year	28	18	26
5 year	50	28	47
ER^-			
Length of therapy			
1 year	6	6	13
2 year	13	7	26
5 year	6	−3	47

*Data from: Early Breast Cancer Trialists' Collaborative Group [38].
[a]Data presented are for ER^+, ER^-, and unknown ER status (combined).

EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP REPORT

While the 1992 meta-analysis performed by the EBCTCG was helpful, it suffered from an inability to compensate for many of the problems associated with the trials of tamoxifen that it analyzed. For example, in the meta-analysis of the data regarding young women and the use of tamoxifen, the absolute number of participants available for analysis in the <50-year-old age group was significantly less than the number in the >50-year-old age group (8,612 vs. 21,280). In addition, the first reported studies of tamoxifen often included both ER^+ and ER^- patients in the same analysis or included large numbers of patients for whom the ER status was unknown. Finally, the duration of tamoxifen therapy in the studies analyzed was often less than the currently accepted 5-year time period.

To address the issue of tamoxifen use in young women, as well as multiple other questions regarding tamoxifen use that still remained unanswered, the EBCTCG undertook an updated review of the worldwide experience with tamoxifen. Beginning in 1995, data regarding any patient involved in a randomized trial of tamoxifen that began prior to 1990 were collected. In 1998, when the latest update was reported, information regarding 37,000 women involved in 55 randomized trials of tamoxifen therapy was available [38]. The trials included both trials of tamoxifen alone vs. no therapy and also trials of tamoxifen plus cytotoxic chemotherapy vs. tamoxifen alone. These data constitute about 87% of all worldwide data regarding this subject and form the basis of a meta-analysis addressing multiple issues surrounding tamoxifen's appropriate use in early breast cancer. A general overview of the results is provided in Table 1.

One of the significant concerns regarding tamoxifen therapy was that of the appropriate time interval for which it should be taken. Prior to the recent meta-analysis, there had been considerable disagreement regarding the optimal duration of therapy. Because of the cytostatic effect of tamoxifen in animal models, it would be reasonable to conclude that a longer duration of therapy should be beneficial [39]. However, several arguments existed against the longer-term use of the agent. These included the fact that patients with metastatic disease tend to progress on therapy after about 1 year, and that studies of adjuvant cytotoxic chemotherapy did not demonstrate a benefit to treatment for longer periods [1,40]. Thus, many early trials included the use of tamoxifen for only 1 or 2 years. However, the 1998 meta-analysis of tamoxifen trials demonstrated clearly that there is an advantage to using tamoxifen for longer periods [38]. In this trial, the proportional reduction in recurrence at 10 years in ER^+ patients was 21, 28, and 50% for treatment of 1, 2, and 5 years, respectively ($2P < 0.00001$). In addition, the proportional reduction in mortality for ER^+ women was 14, 18,, and 28% for treatment for 1-, 2-, and 5-year periods ($2P = 0.018$) (Table I).

A portion of the data that supports the finding that 5 years of therapy is the appropriate period for tamoxifen use comes from two trials that have directly addressed this question. Both of these studies, which have randomized patients to either 2 or 5 years of therapy, have indicated a benefit for the longer treatment period [41,42]. Given these findings and the fact that tamoxifen is a cytostatic agent, some researchers have suggested that tamoxifen therapy for >5 years may be appropriate. However, several groups, including the NSABP, have failed to support its use beyond 5 years [43–45]. None of the trials was able to demonstrate any additional significant benefit to taking tamoxifen beyond the 5-year period. In addition, two of the studies suggested that the

longer duration of therapy might actually be counterproductive [43,45]. Thus, current recommendations should be that treatment continue for 5 years and then be stopped.

In addition to the question of duration of tamoxifen therapy, the issue of its effect on various age groups was readdressed in the most recent overview. As stated previously, the 1992 overview of adjuvant chemotherapy trials failed to reveal any significant benefit of the use of tamoxifen in younger women. However, in a meta-analysis of trials in which 5 years of tamoxifen was used for 5 years, there was a 45% reduction in recurrence rates in women under the age of 50 [38]. This reduction was similar to that in women over 50 and persisted even in women younger than 40 (41% reduction). In addition, this reduction was independent of the menopausal status of the patients. Thus, menopausal status is no longer viewed as an important factor in determining whether a patient should receive adjuvant tamoxifen or not.

While menopausal status no longer appears to be an important factor in determining whether or not an individual patient receives tamoxifen, it is quite clear that the estrogen receptor status of the primary tumor influences the effect of tamoxifen on the reduction in recurrence rates. The majority of the early trials that addressed tamoxifen therapy for early breast cancers did not stratify patients by ER status and included both ER^+ and ER^- patients. One argument for inclusion of all patients has been the various effects of tamoxifen, some of which may not be entirely mediated by the ER. However, the two meta-analyses that have addressed the use of tamoxifen have clearly demonstrated that the effect on recurrence reduction is not significant (NS) in patients with ER^- tumors [37,38]. In the most recent EBCTCG overview, the proportional reduction in risk of recurrence for women with ER^- tumors taking tamoxifen for 1, 2, and 5 years was 6% (NS), 13% ($2P = 0.01$), and 6% (NS), respectively [38]. In addition, the proportional mortality reduction at 10 years in ER^- patients was 6, 7, and −3% for 1, 2, and 5 years of therapy, respectively (NS) [38]. These findings suggest that, whatever effects tamoxifen may exert through non–estrogen-mediated pathways, they are not significant enough to translate into a survival advantage for the patient with ER^- disease.

One final issue regarding therapy with tamoxifen was the question of whether it should be used in conjunction with adjuvant chemotherapy. While the meta-analysis was unable to determine the exact treatment effect of tamoxifen when used in conjunction with systemic chemotherapy, it definitely could demonstrate a clear benefit over use of adjuvant chemotherapy alone. This finding is an extension of the data from the NSABP trial, which showed both a survival benefit and a decrease in recurrence rates in patients taking tamoxifen in addition to systemic chemotherapy [46].

USE OF TAMOXIFEN FOR CHEMOPREVENTION

As physicians obtained more experience with the use of tamoxifen in the treatment of breast cancer, it became evident that it would be an optimal agent to be examined for potential use as a chemopreventive agent. Its efficacy in the treatment of both metastatic breast cancer and of early-stage breast cancer, as well as its low toxicity and good compliance rates [47], supported this theory. As early as a decade ago, its use for the prevention of breast cancer was discussed [48,49]. Several lines of reasoning supported this possibility. First, animal models suggested that tamoxifen may act to prevent both initiation and also promotion of breast cancers [50,51]. Even more compelling was the significant reduction in the incidence of contralateral breast cancers in patients treated with tamoxifen [38,46,52,53]. These findings led researchers in several countries almost concurrently to initiate chemoprevention trials in which tamoxifen was given in an effort to reduce the risk of breast cancer. In the late 1980s and early 1990s, researchers in the United Kingdom, Italy, and the United States enrolled women with no history of breast cancer in trials in which they were randomized to receive either tamoxifen or a placebo for varying periods.

The NSABP conducted the largest of the trials, in which 13,388 women at least 35 years old with a projected risk of breast cancer > 1.66% over a 5-year period were randomized to receive either tamoxifen 20 mg daily or a placebo for a period of 5 years [38,46,52,53]. Risk of any given individual was calculated with a modified Gail model in which age, number of affected first-degree relatives, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche were factored into a risk calculation to determine risk ratios for individuals. Any woman older than 60 who met medical criteria was eligible to participate, as was any woman older than 35 with a diagnosis of lobular carcinoma in situ (LCIS). The results of this trial were revealed early after an independent data-monitoring committee concluded that the results were compelling enough to warrant stopping the trial early. The median follow-up time of all patients analyzed was 54.6 months, with 36.8% having follow-up of >60 months. Of the patients who were randomized in the trial, 23.7% of women in the tamoxifen-treated group stopped therapy, as did 19.7% of women in the placebo group.

There were 368 cases of breast cancer identified in the trial population; 244 of these were in patients taking placebo and 124 were in patients taking tamoxifen. The reduction in risk for both invasive and noninvasive cancers was very similar at about 50%. This reduction in risk was also present in every age group analyzed and was

TABLE II. Comparison of Chemoprevention Trials

Reference First Author	*n*	Hormone replacement therapy	Breast cancer risk
Fisher et al. [55]	13,388	Not acceptable	↑ Over general population
Powles et al. [56]	2,471	Acceptable	↑↑ Over general population
Veronesi et al. [57]	5,408	Acceptable	↑ Or = general population

even greater in patients with atypical hyperplasia (86% reduction) and LCIS (56% reduction). There was a 69% reduction in the annual rate of ER^+ tumors in the group of women taking tamoxifen. However, there was no statistically significant difference in the annual rate of ER^- tumors.

Side effects and complications of the therapy were also noted in the analysis. The likelihood of developing an endometrial carcinoma in this trial was 2.5 times greater in women who received tamoxifen than in women who received a placebo (2.5 cases/1,000 vs. 1 case/1,000). There were 15 endometrial carcinomas identified in the placebo group and 36 identified in the tamoxifen group. Of these, all but 1 (in the placebo group) were FIGO stage I. There was no significant difference in the incidence of ischemic heart disease between the two study populations. There was, however, a 19% reduction in the incidence of fractures in the tamoxifen-treated population, a number that almost reached statistical significance. Pulmonary emboli occurred in 3 times more women in the tamoxifen group than in the placebo-treated group (relative risk [RR] = 3.01; 95% confidence interval [CI], 1.15–9.27). All detrimental effects were seen most often in the group of women over the age of 50.

The second randomized trial of tamoxifen vs. placebo in the prevention of breast cancer was reported from the Royal Marsden Hospital (London, UK) [56]. In this trial, 2,471 women aged 30–70 were randomized to 8 years of either tamoxifen or placebo. A woman was eligible for participation if she had at least one first-degree relative under the age of 50 with breast cancer, or one first-degree relative with bilateral breast cancer, or one affected first-degree relative of any age plus another affected first- or second-degree relative. In addition, women who had undergone a benign breast biopsy and had a first-degree relative of any age with breast cancer were eligible. Median follow-up for this trial was 70 months. There were 336 women in the tamoxifen arm and 305 women in the placebo arm who were also receiving hormone replacement therapy (HRT).

There were 34 cases of breast cancer in the tamoxifen arm and 36 cases in the placebo arm (RR = 1.06; 95% CI 0.7–1.7). The RR of cancer was unchanged when stratified by age group (<50 vs. >50) or by the number of affected relatives. Women who were taking HRT at the time of randomization had an RR of breast cancer of 2 when compared to those not on HRT at randomization. However, there appeared to be no increase in breast cancer risk in the women who started HRT during the trial period. There were 4 cases of endometrial carcinoma in the tamoxifen group and 1 in the placebo group.

The final randomized trial of tamoxifen vs. placebo was performed in Italy [57]. Any woman aged 35–70 years who was medically fit to participate and had undergone a total hysterectomy for reasons other than cancer was eligible for randomization. HRT was allowed. This study included 5,408 women who were randomized to 5 years of either tamoxifen 20 mg daily or placebo. Of the women participating, 12.4% had a first-degree relative with breast cancer. During the treatment and follow-up period, 26.3% of participants withdrew from the study for multiple reasons.

There were 41 cases of breast cancer identified in this trial. Nineteen patients who were taking tamoxifen developed breast cancer and 22 patients on placebo developed breast cancer. Of women who complied with therapy for at least 1 year, there were 19 cases of breast cancer in the placebo group and 11 cases of breast cancer in the tamoxifen group ($P = 0.16$). Fifty-six women who were in the trial developed thrombophlebitis or pulmonary embolus. Six women taking tamoxifen developed deep vein thrombosis compared to 3 women in the placebo group. One woman in each group developed a pulmonary embolus.

As is evident from the data presented here, the two European trials yielded results that were significantly different from those of the NSABP P-01 trial (Table II). Multiple factors are most likely responsible for the differences. First, the number of patients randomized in the European trials was significantly less than that in the NSABP P-01 trial. Thus, the ability of either trial to demonstrate a significant reduction in breast cancer risk is limited by the number of cases of breast cancer expected to develop in each group. The Italian investigators do suggest that there may well be a reduction in risk if women in the trial are followed for a longer period [57]. An additional problem with the small number of women in each of the European trials is the fact that noncompliance has a more dramatic effect upon results. The NSABP was careful to plan for at least 10% attrition with the trial in each year. The Italian investigators did not

TABLE III. Profiles for Chemoprevention of Breast Cancer [55]

Age 35 and
- One first-degree relative with a history of breast cancer, two or more benign biopsies and a history of a breast biopsy showing atypical hyperplasia;
- Or one first-degree relative with a history of breast cancer, two or more benign biopsies, age at first live birth 25 or older, and age at menarche (first menstrual period) 11 or younger
- Or two first degree relatives with a history of breast cancer and a personal history of at least one breast biopsy.

Age 40 and
- Two first-degree relatives with a history of breast cancer and age at first live birth 29 or older;
- Or two first-degree relatives with a history of breast cancer and nulliparous (no children);
- Or one first-degree relative with a history of breast cancer and a personal history of a breast biopsy showing atypical hyperplasia.

Age 45 and
- Two first-degree relatives with history of breast cancer;
- Or one first-degree relative with a history of breast cancer and age at menarche 11 or younger;
- Or one first-degree relative with a history of breast cancer and at least one breast biopsy.

Age 50 and
- One first-degree relative with a history of breast cancer and age at first live birth 20 or older;
- Or history of breast biopsy showing atypical hyperplasia and age at first live birth 20 or older;
- Or history of breast biopsy showing atypical hyperplasia and nulliparous (no children);
- Or history of breast biopsy showing atypical hyperplasia and age at menarche 11 or younger.

Age 55 and
- One first-degree relative with a history of breast cancer;
- Or age at menarche 11 or younger and age at first live birth 30 or older;
- Or history of breast biopsy showing atypical hyperplasia.

Age ≥60

No additional risk factors were required for participation in the Breast Cancer Prevention Trial [55]. However, a woman age ≥50 must consider other factors before choosing to take tamoxifen, such as if she has had a hysterectomy (removal of the uterus). For women age ≥50 in the trial, tamoxifen did increase their chances of three rare but serious health problems: endometrial cancer (cancer of the lining of the uterus) pulmonary embolism (blood clot in the lung), or deep vein thrombosis (blood clots in major veins).

plan for this and, unfortunately, experienced a 26% attrition rate.

A second difference between the European trials and the NSABP P-01 trial was the acceptance of the use of HRT in the European trials. If it is believed that a significant portion, if not all, of tamoxifen's effects are mediated through ER pathways, it is difficult to interpret risk reduction in a population of women taking HRT as well as an antiestrogenic agent.

A final difference among all of the studies concerns the risk profiles of the individual patients involved. In the Italian trial, the only criterion for entry was prior hysterectomy. This requirement ensured that the population would be at less than normal risk of breast disease, as it included women at normal risk (with ovaries intact) and at lower risk (post-oophorectomy). The reduced risk diminishes the likelihood of the accrual of adequate numbers of breast cancer cases to quantify any preventive effect of tamoxifen. At the other end of the spectrum of risk is the British study, in which many women had significant family histories of breast cancer. It is currently unclear what effect, if any, tamoxifen has on women who may have a genetic predisposition to breast cancer [56]. Finally, while the risk for breast cancer development was significant in the NSABP P-01 patients, the majority of women were not believed to be genetically predisposed. Thus, the P-01 trial may be one that best identifies a population in which tamoxifen can be of greatest benefit.

CURRENT USE OF TAMOXIFEN

The role of the surgical oncologist in breast diseases is significant. First, it is often the surgeon who is most involved in the screening of women at increased risk for breast cancer development. In addition, surgeons are likely to be the first physicians to discuss breast cancer treatment options, including nonsurgical treatments, with the patient. Finally, many patients are diagnosed with metastatic breast cancer through biopsies performed by the surgeon. While surgeons may not be the physicians who ultimately write a prescription for tamoxifen, the fact that they play such an integral role in the management of breast cancer mandates that they are aware of all of the indications for its usage.

The majority of patients presenting with metastatic lesions who are known to have ER^+ breast cancer will be treated with tamoxifen. Additionally, this is often first-line therapy in patients with ER^-, progesterone receptor–positive metastatic disease. Any patient presenting with such disease should be considered a candidate for tamoxifen therapy.

The role of tamoxifen in the treatment of patients with early breast cancers has expanded dramatically over the past several years. At present, any patient with an ER^+ invasive breast cancer, regardless of the size of the tumor, should be considered to be a candidate for tamoxifen therapy. In most instances, this will follow systemic

chemotherapy. However, even in patients in whom the tumor is so small that systemic therapy is not warranted, the benefit of tamoxifen in terms of reduction in risk of recurrence and contralateral disease is significant enough to justify consideration of its use. At this time, premenopausal status should no longer be considered a contraindication to its use. Furthermore, patients should be counseled that 5 years of therapy is now considered to be standard.

Currently, there is no consensus on the use of tamoxifen after systemic adjuvant chemotherapy for ER^- tumors. However, it can be argued that while tamoxifen will not benefit the patient in terms of reduction in risk of the index cancer, it may well prevent the growth of a contralateral breast cancer. Thus, patients with ER^- tumors should also be considered candidates for tamoxifen therapy.

Recent data also support the use of tamoxifen for patients who have undergone treatment for ductal carcinoma in situ with lumpectomy and radiation therapy. In the group of patients who received tamoxifen in addition to surgery and radiation therapy, there was a significant reduction in the risk of ipsilateral recurrence and of contralateral disease. Thus, a discussion of tamoxifen in this group of patients is imperative.

Perhaps most confusing to the surgeon is the question of who is a candidate for chemoprevention with tamoxifen. Because the NSABP P-01 trial used a model in which multiple factors were used to determine risk of disease, it is helpful to consider some of the patient profiles that would indicate eligibility for chemoprevention. Table III summarizes the clinical requirements for a patient to be eligible for that trial. It is helpful to keep these criteria in mind when screening high-risk patients. In addition, the National Cancer Institute has developed an easy-to-use computer program to estimate the risk of breast cancer in an individual patient. If time permits, this may help to categorize patients appropriately. Perhaps what is most important for surgeons to recall is that any patient found to have atypical hyperplasia or LCIS in a breast biopsy specimen should be considered a potential candidate for tamoxifen chemoprevention.

CONCLUSION

We are entering a new era in the use of tamoxifen. This drug has become an increasingly important component of the treatment of almost all patients with breast cancer. In addition, it is an integral part of prevention in many patients without breast cancer but with strong risk factors. Because of its relatively low toxicity and good compliance record, it is likely that it will continue to be used as the standard, preferred therapy for many years to come. With the essential role that surgical oncologists play in the diagnosis and treatment of breast cancer, it is imperative that they be aware of the indications for and implications of tamoxifen therapy.

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